Neurobiology of Learning and Memory xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Review

REM sleep and memory reorganization: Potential relevance for psychiatry and psychotherapy

Nina Landmann [a], Marion Kuhn [a], Jonathan-Gabriel Maier [a], Kai Spiegelhalder [a], Chiara Baglioni [a], Lukas Frase [a], Dieter Riemann [a], Annette Sterr [b], Christoph Nissen [a,*]

[a] Department of Psychiatry and Psychotherapy, University Medical Center Freiburg, Germany
[b] Department of Psychology, University of Surrey, UK

ARTICLE INFO

Article history:
Received 18 August 2014
Revised 28 December 2014
Accepted 5 January 2015
Available online xxxx

Keywords:
Sleep
REM sleep
Memory
Reorganization
Associative thinking
Creativity
Psychiatry
Psychotherapy

ABSTRACT

Sleep can foster the reorganization of memory, i.e. the emergence of new memory content that has not directly been encoded. Current neurophysiological and behavioral evidence can be integrated into a model positing that REM sleep particularly promotes the disintegration of existing schemas and their recombination in the form of associative thinking, creativity and the shaping of emotional memory. Particularly, REM sleep related dreaming might represent a mentation correlate for the reconfiguration of memory. In a final section, the potential relevance for psychiatry and psychotherapy is discussed.

1. Introduction

The acquisition of new memories, their strengthening, and their higher-level organization are prerequisites for adaptive behavior in a changing world. In a process of *memory reorganization*, qualitatively new forms of memory can emerge that have not been directly encoded. Recent work suggests that sleep can foster different forms of memory reorganization (Rasch & Born, 2013; Stickgold & Walker, 2013).

In the last century, Sir Frederic C. Bartlett (1886–1969) was the first who systematically investigated the constructive nature of memory (Bartlett, 1932). In his pivotal experiments on repeated reproduction, he observed that text reproductions in humans represent systematically modified versions (reorganizations) of the original text. This observation led him to introduce the concept of *schema* as a framework for the organization and understanding of information. The concept was subsequently extended to the ability of the human mind to systematically organize a multitude of facts and experiences and to extract a general gist that enables the transfer of pre-existing knowledge to novel stimuli and situations (Schacter, 1999; Schacter, Chiao, & Mitchell, 2003). Examples of the constructive nature of memory include observations of erroneous autobiographical memories (Brown & Marsh, 2008), inconsistencies in eyewitness testimonies (Marsh, Tversky, & Hutson, 2005), and memory distortions in patients with mental disorders (Halberstadt et al., 2008).

We recently proposed a multi-process model on the impact of sleep on schema formation, schema integration, and schema disintegration (Landmann et al., 2014). More specifically, schema formation arises from the extraction of rules that can be generalized to novel situations (e.g. Fenn, Nusbaum, & Margoliash, 2003). Schema integration, on the other hand, pertains to the integration of recent and remote memories (e.g. Tamminen, Payne, Stickgold, Wamsley, & Gaskell, 2010), relational memory (e.g. Ellenbogen, Hu, Payne, Titone, & Walker, 2007), and the emergence of false

Abbreviations: REM sleep, rapid eye movement sleep; SWS, slow wave sleep; NREM sleep, non rapid eye movement sleep; ARAS, ascending reticular activating system; LDT, laterodorsal tegmentum; PPT, pedunculopontine tegmentum; PGO waves, ponto-geniculo-occipital waves; EEG, electroencephalogram; CS+, conditioned stimulus; US, unconditioned stimulus; LTP, synaptic long-term potentiation; SFSR hypothesis, sleep to remember sleep to forget hypothesis; fMRI, functional magnetic resonance imaging; PTSD, posttraumatic stress disorder.

* Corresponding author at: Department of Psychiatry and Psychotherapy, University Medical Center Freiburg, Hauptstr. 5, 79104 Freiburg, Germany. Fax: +49 761 270 69190.

E-mail address: christoph.nissen@uniklinik-freiburg.de (C. Nissen).

http://dx.doi.org/10.1016/j.nlm.2015.01.004
1074-7427/

memories (e.g. Payne et al., 2009). The highest level of memory change requires the disintegration and recombination of existing schemas as a prerequisite for the creative use of memory representations on a meta-level in the forms of associative thinking and creativity (e.g. Ritter, Strick, Bos, van Baaren, & Dijksterhuis, 2012) and the processing of emotional memory (e.g. Payne, Stickgold, Swanberg, & Kensinger, 2008). Interestingly, the integration of the literature pointed to a differential impact of the two major sleep stages, slow wave sleep (SWS) and rapid eye movement (REM) sleep, on different forms of memory reorganization. While SWS appears to promote the emergence of a novel gist (schema formation) and the integration of new information into an existing schema (schema integration), REM sleep might particularly facilitate the highest form of memory reorganization, i.e. the disintegration and recombination of existing schemas (Landmann et al., 2014). This model is in accordance with previous theories on memory replay and the emergence of new schemas during SWS (Lewis & Durrant, 2011; Stickgold & Walker, 2013) and their flexible use through activation spreading during REM sleep (Anderson, 1983). Of note, memory reorganization on the behavioral level does not directly inform about the organization of memory traces on the neural level.

The aim of the current work is to further elaborate on the concept of schema disintegration and recombination during REM sleep and to evaluate its potential clinical relevance. We will first highlight REM sleep as a brain state that provides favorable neural conditions for the disintegration and recombination of existing schemas. In the following sections, the impact of REM sleep on the most prominent types of schema disintegration and recombination will be evaluated, i.e. associative thinking, the emergence of creativity and the shaping of emotional memory. Subsequently, the idea that dreaming represents the mentation correlate for the disintegration of existing schemas and an innovative recombination of memory traces will be further discussed. In the final section, potential clinical implications that appear to be of particular relevance for the development and treatment of mental disorders will be put forward.

2. The neurobiology of REM sleep

The transition across the major brain states in mammals, i.e. wake, non rapid eye movement (NREM) sleep and REM sleep, is characterized by profound changes from neural network activity to cognitive processing and motor activity.

Animal studies have revealed the basic mechanisms of sleep regulation (Saper, Scammell, & Lu, 2005). At sleep onset (NREM sleep), both major activating neurotransmitter systems of the ascending reticular activating system (ARAS), the aminergic and cholinergic system, show a substantial reduction of activating inputs to subcortical areas and the cortex. In contrast, REM sleep is characterized by a selective reactivation of cholinergic neurotransmission. Cholinergic neurotransmission arises from the laterodorsal (LDT) and pedunculopontine tegmentum (PPT) in the brain stem, activating the cortex via a thalamic pathway. In addition, cholinergic neurotransmission arises from basal forebrain structures, including the Nucleus basalis Meynert, activating the cortex also via a thalamic pathway but also via direct cortical projections (Jones, 2005). Of note, concurrent activation of limbic and paralimbic structures during REM sleep as part of the cholinergic thalamic pathway, including activation of the amygdala and the anterior cingulate cortex, are crucial for the REM sleep-related generation of emotional states (Pace-Schott & Hobson, 2002).

Intracerebral electrophysiological recordings show phasic endogenous waves, termed ponto-geniculo-occipital (PGO) waves, that are generated in the pons, propagate to the lateral geniculate nuclei of the thalamus, and reach the occipital cortex (Callaway, Lydic, Baghdoyan, & Hobson, 1987; Datta, 1997). These PGO waves are thought to represent the neural basis for the characteristic rapid eye movements during phasic REM sleep and may represent an important mechanism for internally-generated neural activity subtending dreaming (Hobson & McCarley, 1977). Moreover, PGO waves have been linked to brain plasticity and development (Datta, 1999; Peirano & Algarin, 2007; Perogamvros, Dang-Vu, Desseilles, & Schwartz, 2013). For example, in the developing feline visual system, bilateral brainstem lesions that selectively block the generation of PGO waves led to enhanced cortical plasticity during brain maturation as induced by monocular occlusion (Marks, Shaffery, Oksenberg, Speciale, & Roffwarg, 1995).

The electroencephalogram (EEG) during REM sleep in humans (Aserinsky & Kleitman, 1953; Llinas & Ribary, 1993) and animals (Steriade, Amzica, & Contreras, 1996) is characterized by a predominance of EEG activity in the theta range (4–7 Hz) together with high frequency gamma activity (30–80 Hz). Consistent with preclinical findings, brain imaging studies in humans demonstrate a significant increase in regional brain activity in the pontine tegmentum, thalamus, basal forebrain, as well as in limbic and paralimbic structures, including the amygdala and the anterior cingulate cortex (Braun et al., 1997; Maquet et al., 1996; Nofzinger, Mintun, Wiseman, Kupfer, & Moore, 1997). Activation in these limbic and paralimbic regions is consistent with the notion that memory reorganization, and emotional memory in particular, may occur preferentially during REM sleep (Nishida, Pearsall, Buckner, & Walker, 2009; Wagner, Gais, & Born, 2001). In turn, REM sleep might provide specifically favorable conditions for the offline disintegration and reconfiguration of memory traces. However, also other forms of memory organization might occur during REM sleep.

In contrast to the vivid brain activity during REM sleep, alpha motoneuron activity is blocked during healthy REM sleep (Chase & Morales, 1990). On the cognitive level, the activity pattern during REM sleep results in a high waking threshold with a substantially reduced perception of external input, but highly vivid internal mentation ('paradoxical sleep'). This is evidenced, for example, by the often bizarre and highly emotional content of reports from individuals woken up during REM sleep (Manni, 2005).

2.1. Neural networks of memory processing and REM sleep

Memory processing across the sleep-wake cycle is best understood for the declarative memory system and integrated in the *hippocampo-neocortical dialogue model* (Buzsaki, 1996; Power, 2004). This model proposes that newly acquired memories are initially stored in the hippocampus before they are transferred to more permanent neocortical storage sites during NREM sleep. Reactivation of cholinergic neurotransmission during REM sleep largely attenuates this hippocampal readout and, together with a reduction of external sensory input, leads to a functional isolation of limbic/paralimbic structures and the neocortex (Power, 2004; see Fig. 1). Instead of an integration of novel sensory input (waking) or a hippocampal readout and strengthening of memory traces (SWS, Diekelmann & Born, 2010), REM sleep is marked by intracortical spread of neural activation between previously encoded memory representations (Diekelmann & Born, 2010; Giuditta et al., 1995). Thus, similar or associated memory traces might be linked together through changes in synaptic connectivity in localized neural circuits to form a novel network (Anderson, 1983; Tononi & Cirelli, 2003). Moreover, REM sleep might promote local synaptic consolidation, stabilizing the newly built relations between memories (Diekelmann & Born, 2010; Giuditta, Ambrosini, Scaroni, Chiurulla, & Sadile, 1985).

Please cite this article in press as: Landmann, N., et al. REM sleep and memory reorganization: Potential relevance for psychiatry and psychotherapy. *Neurobiology of Learning and Memory* (2015), http://dx.doi.org/10.1016/j.nlm.2015.01.004

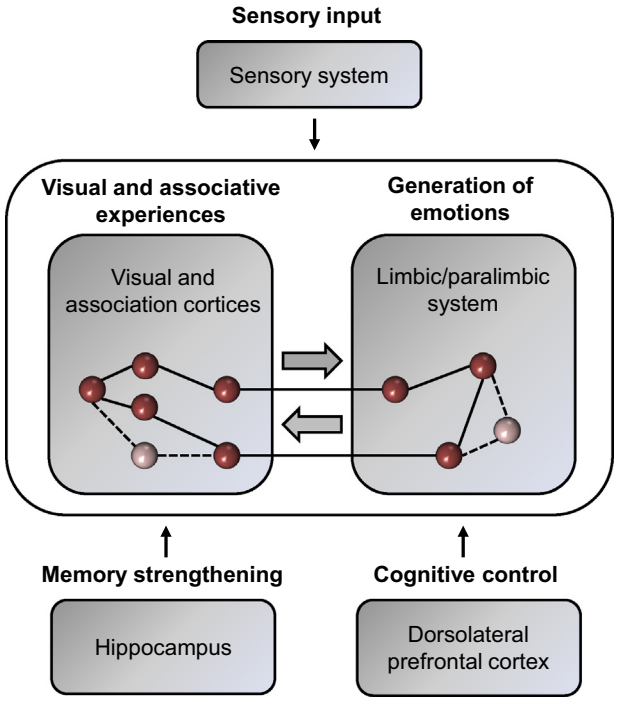

Fig. 1. Memory reorganization in different memory systems during REM sleep. In the declarative memory system, newly acquired memories are initially stored in the hippocampus, before they are transferred to more permanent neocortical storage sites during NREM sleep (memory strengthening). During REM sleep, the hippocampal readout is attenuated, leading to a functional isolation of limbic/paralimbic structures and the neocortex, resulting in intracortical spreading of neural activation between previously encoded memory representations, which may lead to memory reorganization. In contrast to declarative memory, emotional memory processing depends on other neural networks, including emotion processing areas in the amygdala and other networks of the limbic system, that show high activation during REM sleep.

Emotional memory has been shown to depend on different neural networks, particularly on limbic structures, including the amygdala. The most basic and best described model of emotional memory processing is fear conditioning (Phelps & LeDoux, 2005) and fear extinction learning (Hermans, Craske, Mineka, & Lovibond, 2006; Quirk & Mueller, 2008). The association between a conditioned stimulus (CS+) and unconditioned stimulus (US) formed in fear acquisition involves local synaptic long-term potentiation (LTP) in the lateral amygdala (Phelps & LeDoux, 2005). In contrast to fear acquisition, fear extinction refers to the reduction of fear to a CS+ previously linked to an aversive US when the CS+ is repeatedly presented without the US. Notably, fear extinction does not erase the original CS–US association but is a new learning process in which a novel memory trace coexists with the previously acquired CS–US association (Quirk & Mueller, 2008). The extinction of fear, like the initial acquisition, has been shown to emerge from LTP in the lateral amygdala. Also, more complex forms of emotional memory involve activity in limbic and paralimbic structures. As deleniated above, the neural networks that are engaged in the processing of emotional memory show a great overlap with the networks that are activated during REM sleep. This provides some, at least suggestive, evidence for the implication of REM sleep in emotional memory processing.

Lastly, motor learning as part of the procedural memory system also depends on distinct neural circuits and might be influenced by REM sleep (e.g. Plihal & Born, 1997; for an overview see Stickgold, 2005). Motor memory relies on neural plasticity in cortico-subcortical loops (cortico–striato–thalamic–cortical circuits). It is plausible to assume that the schema-modulating function of REM sleep also applies to the reorganization of these networks. This is important for the broad field of motor memory, including habit or sport skill learning in healthy humans and motor rehabilitation after various types of brain lesion. However, the reorganization of motor networks is less relevant for the current focus on psychiatry and psychotherapy.

In summary, REM sleep is characterized by a specific landscape of brain activity that might provide a favorable substrate for the offline reorganization of memories. In the following sections, the effect of REM sleep on the major types of schema disintegration and recombination, i.e. associative thinking, creativity, and the shaping of emotional memory, will be discussed.

3. The impact of REM sleep on associative thinking and creativity

The integration of memories in higher-level schemas often facilitates information processing but might hinder innovative solutions that require out-of-the-box thinking. This is why the disintegration and recombination of existing schemas is a prerequisite for associative thinking and creativity. While associative thinking refers to the formation of new combinations, these can turn into creative solutions when they meet specific requirements or are in some way useful (Mednick, 1962). While creativity might also arise from serendipitous discovery, general requirements for creative solutions include that a person has become stuck on a problem after having unsuccessfully searched for the solution (Kaplan & Simon, 1990; Metcalfe & Wiebe, 1987). After an (offline) incubation period without thinking on the problem, they sometimes achieve a clear and sudden solution, which is accompanied by insight (Bowden & Jung-Beeman, 2003). Several studies indicate that REM sleep can promote associative thinking and creativity.

Earlier studies investigated the effect of sleep deprivation on associative thinking and the ability to find creative solutions, showing that reduced sleep had a negative effect on these forms of memory. For example, priming as an index for associative thinking has been shown to be weakened by sleep deprivation (Babkoff, Genser, Sing, Thorne, & Hegge, 1985; Babkoff et al., 1985). Additionally, one of the first studies investigating more direct measures for creativity showed that participants scored significantly lower on cognitive flexibility and originality after 32 h of sleep deprivation than a control group (Horne, 1988); other studies using different creativity tasks pointed into the same direction (Harrison & Horne, 1999; Wimmer, Hoffmann, Bonato, & Moffitt, 1992). However, these sleep deprivation studies did not inform about the impact of specific sleep stages.

A subsequent line of research centred on the performance after experimental awakening from different sleep stages. These studies demonstrated that associative thinking and creativity is facilitated directly after awakening from REM sleep. In particular, the performance in solving anagram word puzzles was enhanced after awakenings from REM sleep (Walker, Liston, Hobson, & Stickgold, 2002). Moreover, Stickgold, Scott, Rittenhouse, and Hobson (1999) showed that participants were better in learning weak (e.g., *thief – wrong*) but not strong primes (e.g., *hot – cold*) following awakening from REM sleep. Here, weak primes are assumed to resemble remote associations that are often used as an index for creativity. However, it is to note that a REM sleep association is only valid if REM sleep-specific brain activity persists for a certain period of time after awakening (for review, please refer to Dinges, 1990).

A third line of research used pre-post sleep assessments and demonstrated that REM sleep enhances the ability to find remote associations that were primed prior to an experimental sleep/wake condition (Cai, Mednick, Harrison, Kanady, & Mednick, 2009). In this study, participants were tested in the morning and retested

Please cite this article in press as: Landmann, N., et al. REM sleep and memory reorganization: Potential relevance for psychiatry and psychotherapy. *Neurobiology of Learning and Memory* (2015), http://dx.doi.org/10.1016/j.nlm.2015.01.004

in the afternoon after a retention interval that either contained a nap with REM sleep, a nap without REM sleep or a quiet rest period. Whereas no improvement was observed in the NREM sleep and the quiet rest condition, the performance improved by almost 40% after a retention interval with REM sleep relative to baseline. A REM sleep related facilitation in the recombination of formerly distinct schemas has also been confirmed for more valid contexts in which different schemas have to be applied flexibly, including the acquisition of a new language (de Koninck, Lorrain, Christ, Proulx, & Coulombe, 1989) and the processing of a great amount of learning material (Smith & Lapp, 1987).

Performance on these tasks requires the disintegration of familiar schemas and the flexible recombination of separate components across schemas, which enables creative solutions. This facilitation of creativity might result from the functional decoupling of association areas of the cortex from the hippocampus and cognitive control areas, such as the prefrontal cortex, that is characteristic for REM sleep (Fig. 1). This might also be reflected in dream content (e.g. Hobson, Pace-Schott, & Stickgold, 2000; Schwartz & Maquet, 2002)

4. REM sleep and emotional memory

Another important form of memory reorganization is emotional memory processing, for which basic and higher forms can be differentiated. Basic forms pertain to implicit emotional memory in animals and humans, such as classical fear conditioning, for which the emotion is the memory. In contrast, higher forms of emotional memory refer to declarative memories in humans that comprise an emotional component. In this section, we discuss the impact of REM sleep on both forms of emotional memory.

For basic emotional memory, REM sleep deprivation has been shown to have a substantial effect on subsequent *emotional memory encoding* in both animals and humans. Thus, 5 h of REM sleep deprivation prior to training can disrupt avoidance learning in rats (Gruart-Masso, Nadal-Alemany, Coll-Andreu, Portell-Cortes, & Marti-Nicolovius, 1995). In humans, differential effects on emotional reactivity following REM sleep deprivation, with an enhanced reactivity to negative (and a decreased reactivity to positive) material, has been observed. For example, sleep deprivation led to a greater neural reactivity for threat-related emotions (Cote, Mondloch, Sergeeva, Taylor, & Semplonius, 2014; Yoo, Gujar, Hu, Jolesz, & Walker, 2007) and an increased psychophysiological reactivity to negative emotional information measured via pupillography (Franzen, Buysse, Dahl, Thompson, & Siegle, 2009). Moreover, Anderson and Platten (2011) demonstrated that already one night of sleep deprivation results in increased impulsivity to negative stimuli.

In addition, the impact of REM sleep deprivation on *emotional memory processing* has also been investigated. For example, experimental REM sleep deprivation (Fu et al., 2007; Silvestri, 2005) impairs the consolidation of fear extinction learning in rats, with correspondent findings in humans concerning REM sleep deprivation (Spoormaker et al., 2012) and REM sleep disturbances (Spoormaker et al., 2010).

With regard to higher forms of emotional memory, studies suggest that REM sleep may stabilize emotional memory formation in humans by using a split-half paradigm. By comparing early-night (SWS rich) and late-night (REM sleep rich) periods of sleep, some studies demonstrated a retention advantage for REM sleep rich sleep periods for both picture recognition (Groch, Wilhelm, Diekelmann, & Born, 2013; Nishida et al., 2009) and the recall of emotional stories (Wagner et al., 2001). In the latter study, the enhancing effect of REM sleep rich periods was also significant compared to a wake retention interval and even persisted for 4 years (Wagner, Hallschmid, Rasch, & Born, 2006). Importantly, the declarative and the emotional component of the memory have not been differentiated in these studies.

4.1. The 'sleep-to-remember-sleep-to-forget' hypothesis

The 'sleep-to-remember-sleep-to-forget' hypothesis (SFSR; Walker, 2009; Walker & van der Helm, 2009) provides an influential hypothesis on the differential effects of sleep on the memory content and the emotional tone and related memory reorganization. The hypothesis is based on the concept that emotional memory contains two components: the memory content and the emotional tone. When the two components are processed differently, the original memory becomes reorganized. According to the hypothesis by Walker and colleagues (SFSR; Walker, 2009; Walker & van der Helm, 2009), REM sleep strengthens the content and weakens or even removes the emotional tone. Historically, this thought dates back to Sigmund Freud (1856–1939), who postulated that 'dream sleep' (which relates mainly to the sleep stage that was later defined as REM sleep) allows for the processing of emotional memories, leading to a catharsis of exuberant emotions (Freud, 1955). In order to enable flexibility and the adaptation to new situations, the emotional component of a unique memory needs to be detached from its content (schema disintegration and recombination). This is critical to avoid a persistent and automatic reactivation of the initially encoded emotional tone together with situational cues of the content. If this separation of the emotional tone from the memory content is disturbed, mental health problems ranging from depressive mood to clinical disorders may emerge.

In a recent series of studies, Deliens, Gilson, Schmitz, & Peigneux, 2013a; Deliens, Leproult, Neu, & Peigneux, 2013b; Deliens, Neu, & Peigneux, 2013c investigated sleep effects on the unbinding of memories from their emotional tone (Deliens et al., 2013a,b). In one study, the authors designed an interesting experiment in which the encoding of neutral word pairs was coupled with the induction of a specific mood. Here, sleep was found to unbind the memory content from its emotional tone (the learning context) when tested following three nights of sleep (Deliens et al., 2013a). To further test the impact of different sleep stages, they implemented a split-half paradigm and investigated the unbinding of the content and the emotional tone following 3 h of (early) SWS rich sleep in comparison to 3 h of (late) REM sleep with no significant effects (Deliens et al., 2013c). However, it might be possible that the unbinding of the memory content from the emotional tone is initiated during sleep after encoding but is in need of a further passage of time or sleep to fully emerge (Deliens & Peigneux, 2014). This idea is supported by the observation that one night of sleep with several NREM-REM sleep cycles is not sufficient to suppress mood-dependent memory effects (i.e. interference with the recall of information learned in a happy or sad mood), showing that the unbinding of memories from their emotional tone needs several nights to fully emerge (Deliens & Peigneux, 2014). Yet, other studies suggest that REM sleep decreases the emotional reactivity to aversive or stressful experiences. For instance, subjectively rated reactivity in a fear recognition task was attenuated following a nap containing REM sleep, with reverse effects after a nap without REM sleep or a wake period of equal length (Gujar, McDonald, Nishida, & Walker, 2011a). Furthermore, emotional distress has been observed to cause alterations in the REM sleep pattern, which was associated with less emotional attenuation over sleep (Talamini, Bringmann, de Boer, & Hofman, 2013).

The notion of a (REM) sleep-specific decrease of the emotional tone is not unequivocally supported. Thus, several studies did not confirm a decrease of the emotional tone following REM sleep, with some studies even pointing toward an increase in emotional

Please cite this article in press as: Landmann, N., et al. REM sleep and memory reorganization: Potential relevance for psychiatry and psychotherapy. *Neurobiology of Learning and Memory* (2015), http://dx.doi.org/10.1016/j.nlm.2015.01.004

reactivity after sleep (e.g. Baran, Pace-Schott, Ericson, & Spencer, 2012; Groch et al., 2013; Wagner, Fischer, & Born, 2002). For example, a shift toward enhanced negative ratings after REM sleep (Wagner et al., 2002) and, complementary, reduced negative ratings following a high, in contrast to low, percentage of REM sleep deprivation has been reported (Lara-Carrasco, Nielsen, Solomonova, Levrier, & Popova, 2009).

With regard to potential neural correlates, the findings at hand are equally contradictive: while an fMRI study demonstrated a reduction of amygdala activation following sleep in response to familiar negative pictures (van der Helm et al., 2011), an amplified amygdala response to negative emotional material following sleep deprivation was observed in another study (Yoo et al., 2007).

What appears to be contradictive might be unified if the schema concept is taken into consideration. Specifically, REM sleep may strengthen or weaken the newly acquired emotional memory component depending on how strongly the emotion is integrated into a schema. For example, after classical fear acquisition, the emotion fear might be tightly linked to a CS+ (e.g., a spider shown to individuals with spider phobia) and might be stabilized or even enhanced during REM sleep. Similarly, in successful extinction learning, a new and stable memory (or schema) without the negative emotion is built that might also be stabilized during REM sleep (Spoormaker et al., 2010, 2012).

In contrast, if the emotion is not very tightly integrated into a schema, as in some laboratory studies that comprise declarative memory content and an emotional tone, the emotional component might be weakened or even removed during REM sleep (Gujar et al., 2011a; Gujar, Yoo, Hu, & Walker, 2011b).

4.2. Neural mechanisms

In order to further reveal potential neural mechanisms, the impact of specific sleep characteristics on emotional memory formation has been investigated. Several studies examined the interplay of REM sleep and fear conditioning. Thus, fear conditioning affects post-training REM sleep. Specifically, the duration of REM sleep and the number of REM sleep episodes were decreased, while REM sleep latency was increased after fear acquisition training in rats (Sanford, Silvestri, Ross, & Morrison, 2001). In turn, REM sleep characteristics affect post-sleep fear memory. Particularly, both SWS and REM sleep were increased following fear extinction training in rats. However, only the animals that exhibited an increase in phasic pontine-wave activity during post-training REM sleep retained fear extinction memory 24 h later (Datta & O'Malley, 2013).

Early electrophysiological studies (e.g. McCarley, Winkelman, & Duffy, 1983) and recent brain imaging studies (e.g. Miyauchi, Misaki, Kan, Fukunaga, & Koike, 2009; Wehrle et al., 2005) provided indirect evidence that PGO waves during REM sleep also occur in humans. However, future studies are needed to further characterize their physiology and function in humans.

Other studies demonstrated that the duration of post-learning REM sleep in general and an increase in EEG theta activity during REM sleep in particular were positively correlated with emotional memory consolidation, e.g. emotional picture recognition in humans (Nishida et al., 2009) and conditioned fear memory in rats (Popa, Duvarci, Popescu, Lena, & Pare, 2010). Importantly, these studies did not differentiate between the content and the emotional component and most studies did only use material with a negative valence.

Moreover, REM sleep-related neurochemical changes may also be implicated. For example, an acetylcholine-dependent reactivation of the amygdala, in the absence of noradrenergic activity, has been described (van der Helm et al., 2011). Finally, as mentioned, emotional memory and REM sleep appear to share similar neural activation patterns, such as a high limbic system activation (Vuilleumier, 2005; Walker & van der Helm, 2009). Together, these observations support a role of REM sleep in the processing of emotional memories.

5. REM sleep and dreaming

Dreaming, especially during REM sleep, might be implicated in memory reorganization. However, despite the fascination for dreams that dates back to the beginning of mankind and the subsequent multitude of studies (e.g. Barbera, 2008), the exact mechanisms and functions of dreaming remain debated (Blagrove, 2009; Nielsen, 2000). This does not come as a surprise, since the relevant questions refer to the classic debate on the interplay between the neurochemistry of the brain and the emergence of cognition and consciousness. As a general methodological shortcoming, it is to note that dream reports are subjective and retrospective in nature and, thus, highly suggestible to different types of bias, including e.g. a mood-dependent recall. In the following paragraphs, we will outline the main concepts (a mind-focused, a biological and an integrational concept) and discuss them in the context of memory reorganization.

Dream mentation is characterized by internally generated sensory-motor, cognitive and emotional experiences during sleep (Desseilles, Dang-Vu, Sterpenich, & Schwartz, 2011). Even though dreams are not exclusively experienced during REM sleep, this brain state facilitates dreaming and descriptions of vivid experiences mainly occur after awakenings from REM sleep (Antrobus, 1983; Foulkes, 1985). Thus, dreaming might be best described along a continuum, from thought-like mentation (typical for SWS) to vivid, bizarre and highly emotional experiences (typical for REM sleep; Cavallero, Cicogna, Natale, Occhionero, & Zito, 1992; Stickgold, Malia, Fosse, Propper, & Hobson, 2001), with a predominance of negative emotions during REM sleep dreaming (e.g. Merritt, Stickgold, Pace-Schott, Williams, & Hobson, 1994; Nielsen, Deslauriers, & Baylor, 1991).

Interestingly, already more than 200 years ago, the idea has arisen that dreaming might have an impact on associative memory (Hartley, 1801; Lavie & Hobson, 1986). To our knowledge, the first direct evidence was provided by the French sinologist Hervey de Saint-Denys (1867/1977), who showed that his memories were reflected in his dreams. In his experiment, he asked his servant to put a perfume used on a previous trip on his pillow during sleep (single-blind design). He found that the odor could reactivate vivid dreams of the previous trip and this effect was even robust over several months. Accordingly, analyses of dream content revealed that aspects of past and current waking-life experiences are common in dreams (Foulkes, 1962; Schwartz, 2003) and are often combined in novel ways (Rittenhouse, Stickgold, & Hobson, 1994), with an exact replay of waking experiences just being found in 1–2% of dream reports (Fosse, Fosse, Hobson, & Stickgold, 2003). These findings additionally emphasize the disintegrative and recombining character of dreams.

Besides just reflecting ongoing processes of memory reorganization, some authors have recently hypothesized that dreaming itself might serve an adaptive function for the organism (e.g. Desseilles et al., 2011; Revonsuo, 2000). In the domains of problem solving and creativity, a multitude of anecdotal reports describe the emergence of creative solutions during dreams (Mazzarello, 2000). A systematic dream content analysis revealed that 25% of college students' dreams provide a solution for a problem not found during waking (Barrett, 1993), and a study with 444 participants reported that about 8% of all dreams stimulated waking-life creativity and emotional insights (Schredl & Erlacher, 2007). Also, with regard to emotional memory processing, several studies indi-

Please cite this article in press as: Landmann, N., et al. REM sleep and memory reorganization: Potential relevance for psychiatry and psychotherapy. *Neurobiology of Learning and Memory* (2015), http://dx.doi.org/10.1016/j.nlm.2015.01.004

cate that dreaming itself (beyond REM sleep) might contribute to processing and handling emotions at wake time which enables for adaptive behavior (Nielsen & Levin, 2007).

Besides research focusing on subjective dream reports, the discovery of REM sleep in the 1950s (Aserinsky & Kleitman, 1953; Dement & Kleitman, 1957) and an impressive progress in brain research in the following decades, supported a high optimism into the potential of the neurosciences to reveal the final answers to the brain-mind interplay. In contrary to the subjective approach presented above, important basic science studies put forward the idea that dreaming is a random by-product of REM sleep physiology (Hobson & McCarley, 1977). According to the simplest version of this concept, dreaming does not entail any relevant information about memory reorganization; mentation during REM sleep is regarded as a mere epiphenomenon of electrophysiological noise. Although recent work suggests that this concept is too reductionist, it is important to note that, at the time, the biological perspective represented an important innovation that helped to overcome a purely mind-focused perspective that did not link mentation to state-dependent brain physiology (Flanagan, 2000; Solms, 1997).

The integrative concept highlights that dream-like mentation emerges from the specific neurobiological milieu of REM sleep, while taking into account that dream mentation during REM sleep, beyond random noise, is linked to prior individual experiences, with memory traces being reactivated and reprocessed in a meaningful way (Hobson, 2009; Hobson et al., 2000).

Over the past decades, the use of modern brain imaging techniques has offered further inroads to investigate the neural mechanisms of dreaming. Interestingly, several brain regions have been reported to show reduced activity during REM sleep in comparison to wakefulness. Particularly, the prefrontal and parietal cortex, regions that subserve important executive and attentional functions during wakefulness, have been reported to be deactivated during REM sleep (Maquet, 2005; Maquet et al., 2005). This might result in the bizarre and illogical reconfiguration of dream elements (e.g. Hobson et al., 2000; Schredl & Erlacher, 2007; Schwartz & Maquet, 2002). In addition, a deactivation of the dorsolateral–prefrontal cortex and the inferior parietal lobe during REM sleep might explain why external stimuli are either ignored or automatically incorporated into the dream narrative rather than interrupting the dream storyline (Burton, Harsh, & Badia, 1988; Desseilles et al., 2011; Foulkes, 1966). In this vein, Desseilles et al. (2011) hypothesized that the activation of isolated episodic elements on the mental level (Fosse et al., 2003; Schwartz, 2003), in correspondence with the activation of limbic structures and a deactivation of the dorsolateral–prefrontal cortex, results in the creation of new associations and the reorganization of experiences during dreaming.

Together, despite some progress, the function of dreams in the process of memory reorganization remains to be further specified. Dreaming during REM sleep might facilitate novel solutions and adaptive behavior under certain circumstances; yet under other circumstances these effects could not be demonstrated. Further research is needed to determine the factors under which dreaming facilitates novel solutions and adaptive behavior as a prerequisite to translate this understanding into clinically meaningful interventions.

6. REM sleep – does it have all the answers?

While a multitude of studies that highlight the importance of REM sleep for memory reorganization in general and schema disintegration and recombination in particular, current evidence is not without contradictions. For example, although numerous studies demonstrate a sleep-dependent effect on memory reorganization in the forms of associative thinking, creativity, and emotional memory processing, a specific role of REM sleep could not consistently be demonstrated (e.g. Baran et al., 2012; Ritter et al., 2012; Sio, Monaghan, & Ormerod, 2013). While the separate processing of the memory content and the emotional tone could be confirmed (Deliens et al., 2013a), the findings on the impact of sleep are contradictory and not always in line with the SFSR hypothesis (e.g. Baran et al., 2012; Deliens et al., 2013a; Groch et al., 2013). There is also a divergence of findings on the neural level, with some fMRI studies demonstrating increased (Payne & Kensinger, 2011; Sterpenich et al., 2009) rather than decreased amygdala activity (Payne & Kensinger, 2011; Sterpenich et al., 2009) for emotionally aversive pictures presented following sleep. In addition to the strength of the emotional tone, which might influence subsequent processing (see also Section 4), the effects may also be time-dependent, with a reduction in affect requiring more time to evolve than the length of the retention interval (compare the study by Deliens et al. (2013a,b,c) with the re-test after 3 nights of sleep and Deliens et al. (2013a,b,c) with the re-test after a few hours). This argument is further strengthened by the observation that the superiority of emotional over neutral memories is also pronounced after longer time intervals (Dolcos, LaBar, & Cabeza, 2005; Wagner et al., 2006). In order to integrate the diverging results, REM sleep may favor adapted emotional responses with a reduction or an increase in the emotional tone, depending on the circumstances and the experimental set-up (Desseilles et al., 2011).

Importantly, there may also be an interaction of SWS and REM sleep on emotional memory processing (Cairney, Durrant, Power, & Lewis, 2014; Talamini et al., 2013; Wagner et al., 2002). For example, Wagner et al. (2002) demonstrated a reverse effect of REM sleep and SWS, with a trend toward more positive ratings after SWS and complementary, enhanced negative ratings after REM sleep in a split-half night time paradigm.

Moreover, future research is needed to determine the causes and the impact of substantial inter- and intra-individual (across nights) variability during REM sleep and its profound changes across development.

The potential implications of REM sleep-related memory reorganization for psychiatry and psychotherapy will be discussed in the final section.

7. The relevance for psychiatry and psychotherapy

The impact of REM sleep on memory reorganization might have important implications for psychiatry and psychotherapy. On the one hand, disturbed sleep and especially disturbed REM sleep may be implicated in the development of mental disorders. Vice versa, the manipulation of REM sleep, also in combination with psychotherapy, may offer new perspectives for the treatment of mental disorders.

7.1. Alterations of REM sleep might impair memory reorganization and mental health

In line with the studies presented, REM sleep disruptions may impair an adequate organization of memories, particularly in terms of emotional memories. This may either facilitate the onset or worsen the course of a mental disorder. However, only indirect evidence derived from short-term sleep deprivation studies or observational longitudinal studies exist because chronic experimental sleep disruption in humans is not possible due to ethical considerations.

Short-term sleep deprivation can have a negative impact on mood, with a shift toward disturbed processing of emotionally positive memories and a relative robustness of emotionally

Please cite this article in press as: Landmann, N., et al. REM sleep and memory reorganization: Potential relevance for psychiatry and psychotherapy. *Neurobiology of Learning and Memory* (2015), http://dx.doi.org/10.1016/j.nlm.2015.01.004

negative memories (Cote et al., 2014; Gujar et al., 2011b; Yoo et al., 2007). However, other studies showed the opposite, with emotional reactivity to negative material being preserved or even enhanced following REM sleep (e.g. Baran et al., 2012; Cartwright, 1974; Wagner et al., 2002). In line with these studies, emotional reactivity to negative material was reduced (and not enhanced) following REM sleep deprivation (Lara-Carrasco et al., 2009). Another study demonstrated that self-appraisals of patients with depression and anxiety disorder were significantly more negative after experimental awakenings from REM sleep in comparison to awakenings from NREM sleep, pointing to an implication of REM sleep in the regulation of mood (McNamara, Auerbach, Johnson, Harris, & Doros, 2010).

In contrast to the conflicting findings of short-term sleep deprivation, longitudinal studies on sleep and mental disorders draw a clearer picture. Here, primary insomnia, i.e. chronic sleep disruptions in the absence of another disorder, has been identified as an independent risk factor for the de novo onset of a mental disorder, such as major depression (Baglioni et al., 2011). Moreover, insomnia has been identified as a predictor for depression and anxiety after an acute brain trauma (Rao, McCann, Han, Bergey, & Smith, 2014). Furthermore, sleep disturbances, particularly of REM sleep, are predictive for the development of post-traumatic stress disorder (PTSD; Lavie, 2001; Mellman, Pigeon, Nowell, & Nolan, 2007), with an increased risk for the development of PTSD in trauma-exposed individuals with a shorter averaged duration of REM sleep periods (Mellman et al., 2007). With regard to major depression, changes in REM sleep, such as an increased REM density and reduced REM latency, have been reported to precede clinical depression (Giles, Kupfer, Rush, & Roffwarg, 1998; Gottesmann & Gottesman, 2007). However, it is not clear if these changes in REM sleep constitute a trigger or an early symptom of depression or, alternatively, a compensatory effort to restore a lost equilibrium.

To further understand the mechanisms, it is of interest to investigate the relationship between mood and sleep in the opposite direction, i.e. the influence of emotionally distressing experiences on subsequent REM sleep (Lavie, 2001). Studies focusing on critical life events such as divorce (Cartwright, 1983) or spousal bereavement following death (Reynolds et al., 1992, 1993) equally show alterations of REM sleep patterns, with a shortening of REM sleep latency and an increase in REM density, indicating a causal influence of emotionally negative events on REM sleep patterns. An experimental study in healthy participants demonstrated altered REM sleep pattern in terms of an absence of the normally observed REM sleep increase over the course of the night, together with an increased number of REM sleep periods, following the presentation of emotionally distressing films in the evening that predicted a disruption of the attenuation of emotions after sleep (Talamini et al., 2013). This indicates that changes of REM sleep might mediate dysfunctional mood regulation. Another study demonstrated an overnight reduction in depressed mood following an increased number of REM sleep periods induced by experimental REM sleep awakenings. This is in line with the concept of a rather protective function of REM sleep disruptions (Cartwright, Baehr, Kirkby, Pandi-Perumal, & Kabat, 2003). Future studies are needed to further clarify the impact of different aspects of REM sleep (latency, phasic events, continuity) on the regulation of mood and memory. Particularly, the elucidation of sleep-related effects on the processing of traumatic events and on the risk of developing PTSD would be of great interest (Wittmann, Schredl, & Kramer, 2007).

When a PTSD has already developed, emotionally intensive dreams, in particular nightmares, often disrupt the maintenance of REM sleep (Nielsen & Levin, 2007). On the neurophysiological level, this results in dissociated sleep features, such as partial arousals during REM sleep (Howell, 2012). These arousals during REM sleep might represent an early attempt of the organism to cope with an emotionally stressful event. If the event is too stressful, the organism might fail to handle the experiences despite the REM sleep alterations, which may result in a mental disorder. In this case, REM sleep alterations might even have an inverse, i.e. negative effect on the disorder. This is in line with a model proposed by Stickgold (2007), in which the near-veridical re-enactments of the trauma in the form of nightmares and disrupted REM sleep in PTSD may relate to a blockade of the normal modification and reinterpretation of emotionally salient memories.

In line with our model, a normal REM sleep pattern, i.e. a REM sleep pattern that is not substantially altered by internal or external influences in the context of e.g. a mental disorder or drugs, enables for successful schema disintegration and recombination, which represents a prerequisite for attenuated emotional reactivity to the traumatic event. We therefore hypothesize that improving sleep in PTSD, and REM sleep in particular, might facilitate an adequate trauma processing and improve the condition.

Taken together, REM sleep seems to play an important, yet contradictory role in emotional memory processing. But when do alterations of REM sleep trigger disturbed mood or a mental disorder, when are they a mere epiphenomenon and when do they represent a compensatory mechanism preventing or improving a disorder? Hitherto, no overarching model is available to explain the diverging results. With regard to our schema model, it may be possible that mental disorders are, in part, the result of a dysregulation of schema disintegration and recombination, which is modulated by sleep.

7.2. Manipulations of REM sleep as therapeutic interventions

Sleep-related interventions may provide new inroads into the prevention or treatment of mental disorders. In the following paragraphs, we will give an overview of the first approaches into this direction and discuss some new ideas.

The development and maintenance of mental disorders may be influenced by sleep. First evidence for a REM sleep-specific effect on the formation of fear memories was provided by Menz et al. (2013). Recall of learned fear, as indicated by subjective (perceived anxiety) and objective (autonomous nervous) responses, was positively correlated with the preceding time spent in REM sleep and paralleled by activation of the basolateral amygdala. In this context, REM sleep deprivation following stressful events could be implemented as a therapeutic tool to impair the formation of fear memories. This is of great relevance concerning the development of anxiety disorders, including PTSD (Walker & van der Helm, 2009). Direct evidence pointing into this direction was delivered in a recent animal study in which fear memory was impaired by sleep deprivation in rats (Kumar & Jha, 2012).

In order to further pursue this interesting approach, it is important to gain more insight into the effects of the timing of sleep following emotional events. In animals, 'REM windows' with increased amounts of REM sleep have consistently been found for procedural learning tasks with an emotional component, in which REM sleep deprivation leads to diminished retention (Smith, 1985). Fear learning could be selectively impaired by sleep deprivation between the first 0 and 5 h following training. However, between 5 and 10 h, no effect could be observed (Graves, Heller, Pack, & Abel, 2003). If these findings can be transferred to humans, immediate sleep deprivation following a trauma might prevent the development of PTSD by attenuating the consolidation of negative memories (Walker & van der Helm, 2009). In line with this hypothesis, the National Sleep Foundation's 'Sleep in America' Poll (2002) reported that the events of September 11 had a dramatic impact on the quality of Americans' sleep, with about 69% of Americans suffering from insomnia in the nights immediately

Please cite this article in press as: Landmann, N., et al. REM sleep and memory reorganization: Potential relevance for psychiatry and psychotherapy. *Neurobiology of Learning and Memory* (2015), http://dx.doi.org/10.1016/j.nlm.2015.01.004

following the attacks. Yet only a small proportion of these people developed PTSD and the highly prevalent sleep disruption after the traumatic events might have even served as a protective mechanism, attenuating an imminent over-consolidation in a sort of 'self-therapy'.

Initially counterintuitive, but consistent with this line of reasoning, one might speculate that short-term sleep deprivation or the deprivation of particular sleep stages immediately after a trauma along with intentionally increased interference may be used therapeutically to prevent the extreme consolidation of new and initially instable traumatic memories. In contrary, sleep immediately following psychotherapy could stabilize or even augment therapeutic effects, and enable the new and flexible use of the individual's schemas. Interestingly, recent and influential developments in cognitive behavioral therapy, such as schema therapy (Young, Klosko, & Weishaar, 2003) or the Cognitive Behavioral Analysis System of Psychotherapy (CBASP; McCullough, 2000, 2006), implement the idea of schemas as a commonly used concept to describe cognitive and emotional structures.

Two recent studies investigated the effect of sleep following exposure psychotherapy (Kleim et al., 2014; Pace-Schott, Verga, Bennett, & Spencer, 2012). Following a night of sleep (Pace-Schott et al., 2012), but also after brief periods of daytime sleep immediately following exposure therapy (Kleim et al., 2014), significant decreases in fear in patients with spider phobia were observed. With this concept, it should be possible to enhance psychotherapeutic effects by periods of sleep following psychotherapy. This might specifically apply to exposure therapy. Of note, within-session habituation does not predict (and may even counter) between-session consolidation of extinction (Craske et al., 2008).

Another approach is the direct manipulation of sleep. For example, the presentation of a conditioned sound (Antony, Gobel, O'Hare, Reber, & Paller, 2012; Rudoy, Voss, Westerberg, & Paller, 2009) or an odor (Rasch, Buchel, Gais, & Born, 2007; Ritter et al., 2012) during sleep has been shown to improve memory performance or even creativity (Ritter et al., 2012). This approach could already be transferred to a clinical setting, with one study showing that fear extinction memory which was conditioned with an odor could be promoted by the re-exposure to the odor during sleep (Hauner, Howard, Zelano, & Gottfried, 2013). Moreover, Ritter et al. (2012) provided evidence that is possible to actively support creativity and the flexible use of schemas by presenting a conditioned odor during sleep. Interestingly, the participants who were exposed to the odor were not only found to be more creative, but they were also better able to select their most creative idea as a correlate for the ability to flexibly use schemas. These findings may also have implications for patients with mental disorders in which the flexible use of schemas is important. This is for instance the case for obsessive compulsive disorder and a wide range of personality disorders, such as borderline personality disorder. If the process is disturbed, dysfunctional behavior may result, such as in fear and anxiety disorders, in which singular experiences are generalized to new, de facto harmless situations, or in PTSD, in which a single cue is sufficient to trigger a cascade of traumatically loaded experiences. In the context of schema therapy (Young et al., 2003), the aim is to re-enable the individual to flexibly use different schemas, e.g. by segregating disadvantageous conjunctions between the schema content and the emotional tone. In that sense, schema therapy and REM sleep share the functional mechanism of dissociating the memory content and the emotional tone, which could be further augmented by sleep following a therapeutic session.

Furthermore, modulation of sleep-specific brain activity patterns has been shown to affect memory consolidation (Girardeau, Benchenane, Wiener, Buzsaki, & Zugaro, 2009; Marshall, Helgadottir, Molle, & Born, 2006; Ngo, Martinetz, Born, & Molle, 2013). In accordance with this line of research, one recent study showed that in patients with schizophrenia, the modulation of sleep-specific brain activity patterns during sleep could enhance declarative memory processing (Goder et al., 2013).

In animals, extinction training results in an increase of PGO waves, which seem to be implicated in the consolidation of fear extinction memory (Datta & O'Malley, 2013). If this finding can be transferred to humans, the increase of PGO waves may be a promising therapeutic technique to stabilize or augment the therapeutic effects following exposure therapy. Interestingly, the selective muscarinic M1 acetylcholine receptor agonist RS-86 has been shown to selectively enhance the number of rapid eye movements (as a presumed correlate of PGO waves) in healthy individuals, without changing REM sleep duration (Nissen et al., 2006a). This manipulation did not modulate neutral declarative or motor memory consolidation during sleep (Nissen et al., 2006b). Studies on other types of memory, including different forms of memory reorganization, have not been conducted.

On the mental level, the manipulation of dreaming may offer another opportunity to increase psychotherapy. In PTSD, one of the central symptoms is the persistence of fear-provoking memories patients are unable to extinguish, often reoccurring in nightmares (Anderson & Insel, 2006; Rothbaum & Davis, 2003). Typically, the dreamer remains unaware of being in a dream (Johnson, Kahan, & Raye, 1984). In contrast, lucid dreaming is a state in which the dreamer is actually conscious of being in a dream (Cicogna & Bosinelli, 2001). This offers the dreamer the ability to manipulate the content of the ongoing dream and, accordingly, the emotional tone. In the context of e.g. PTSD, the emotionally negatively loaded content may be changed, thus restructuring the trauma. Another, therapeutic approach in the treatment of PTSD is Imagery Rehearsal Therapy, in which nightmares are visualized during the therapy with the idea to change negative schemas (Krakow & Zadra, 2006; Moore & Krakow, 2007).

In addition, the effects of psychotherapy might also be modulated by the sleep-related administration of psychotropic drugs. For example, the administration of dopaminergic agents in humans elicits vivid dreams (Balon, 1996; Pinter, Pogarell, & Oertel, 1999; Thompson & Pierce, 1999), which in combination with lucid dreaming could help to strengthen desired therapeutic effects. In contrast, the administration of D2 antagonists, which is associated with a reduction in vivid dreaming (Gaillard & Moneme, 1977) and nightmares (David, de Faria, Lapeyra, & Mellman, 2004; Jakovljevic, Sagud, & Mihaljevic-Peles, 2003; Lambert, 2006), may be helpful to lighten PTSD symptoms and possibly prevent the development of PTSD in an early phase following the trauma. Also, it has been shown that blocking cortisol during sleep enhances the consolidation of negative memories (Wagner, Degirmenci, Drosopoulos, Perras, & Born, 2005). Given that cortisol secretion is low in patients with PTSD, low cortisol levels especially during REM sleep in the early morning hours might contribute to a reinforcement of negative emotional content. Based on these findings, one can speculate that the synthetic enhancement of cortisol secretion, e.g. corticotrophin-releasing factor during the night, could attenuate or even prevent the processing and consolidation of emotionally negative memories. Another promising target represents the modulation of the noradrenergic neurotransmitter system, for example with the alpha1 receptor agonist prazosin (Broese, Riemann, Hein, & Nissen, 2012).

Finally, the close relationship between sleep and mood disorders, in particular the therapeutic effect of sleep deprivation in major depression, has been proposed to be mediated by the suppression of REM sleep (Vogel, Vogel, McAbee, & Thurmond, 1980). However, subsequent studies did not unequivocally corroborate a therapeutic effect of selective REM sleep deprivation in

Please cite this article in press as: Landmann, N., et al. REM sleep and memory reorganization: Potential relevance for psychiatry and psychotherapy. *Neurobiology of Learning and Memory* (2015), http://dx.doi.org/10.1016/j.nlm.2015.01.004

Table 1
REM sleep dependent memory reorganization – main findings.

Associative thinking and creativity
- Negative effects of REM sleep deprivation on priming (as an index for associative thinking) and creativity (no information on specific sleep stages)
- Enhanced associative memory following REM sleep awakenings (measured by anagram word puzzles and weak primes)
- Enhanced creativity following REM sleep naps (as performance in formerly primed RAT items)

Emotional memory processing
- REM sleep deprivation prior to learning impairs memory encoding and enhances reactivity to negative emotional material
- REM sleep deprivation following learning impairs the processing of basic forms of learning in both animals and humans
- REM sleep promotes the consolidation of emotional memory content
- REM sleep effects the emotional tone of a memory, with some studies pointing to a decrease, some studies to an increase of the emotional tone following REM sleep

REM sleep dreaming
- dreamlike-mentation emerges from the specific neurobiological milieu of REM sleep
- Dreaming has a recombining and reorganizing character, which either passively reflects underlying processes or actively reorganizes memory
- A relationship between dream content and subsequent, as well as preceding mood could be found

patients with major depression and emphasized a collateral impact on SWS homeostasis of the procedure (e.g. Reynolds et al., 1990). Subsequent lines of research rather point to the concept that changes in SWS homeostasis and related synaptic plasticity processes might drive the therapeutic effect of sleep deprivation in major depression (Castren, 2005). Similarly, the suppression of REM sleep by many antidepressants has been shown to be transient in nature (with a normalization of REM sleep after several weeks of constant medication) and might rather represent an epiphenomenon of an earlier treatment phase than a causal component of the long-term clinical efficacy (Riemann, Berger, & Voderholzer, 2001).

8. Conclusions

The current article provides an overview of the impact of REM sleep on memory reorganization. The studies reviewed suggest that REM sleep modulates higher-order forms of memory reorganization. Schema disintegration and recombination is a critical prerequisite for humans to adapt to changing environments. REM sleep seems to be significantly implicated in this ability. Current evidence pertains to the areas of associative thinking and creativity, as well as emotional memory processing. The role of dream mentation and its function in the process of memory reorganization has been further discussed. REM sleep specific neural processes have been presented and related to the behavioral level.

In summary, manifold evidence confirms that REM sleep supports the flexible use of memories by promoting the disintegration and recombination of existing schemas. However, it remains an unresolved question under what conditions REM sleep has what implications. For example, when does REM sleep enhance, and when does it reduce the affective tone of an emotional memory? Due to the inconsistent findings, the behavioral effects observed seem to be fragile and may only emerge under specific experimental conditions, as e.g. including for instance the experimental design, the material applied, and the duration of REM sleep. The underlying neural processes should be further elucidated. Also, the role of SWS in the process of schema disintegration and recombination and a potential interaction with REM sleep is particularly unclear.

Furthermore, the function of dreaming is still dubious. For example, no study has ever been able to directly relate emotions experienced in dreams to correspondent brain activations. This is why future research is needed to shed more light on the underlying neurophysiological mechanisms of REM sleep and its interaction with dream mentation and how they might contribute to schema disintegration and recombination and the modification of the emotional impact of past experiences.

A normal REM sleep pattern is critical for mental health and accordingly, REM sleep-related interventions might have the potential to improve relevant health outcomes. Memory reorganization, especially in terms of emotional processing, plays a crucial role for mental health and well-being. Specifically, the adequate processing of emotions, which seems to be critically modulated by REM sleep, is a prerequisite to enable adaptive behavior. If this process in turn is disturbed, mental disorders, such as PTSD, may occur. Together, the evidence reviewed indicates that sleep in general does not guarantee for memory reorganization. Rather, specific REM sleep dependent physiological events may promote memory reorganization (see Table 1).

Acknowledgments

Nina Landmann has been supported by a PhD grant provided by the Cusanuswerk. Marion Kuhn has been supported by a PhD grant provided by the FAZIT Stiftung.

References

Anderson, J. R. (1983). A spreading activation theory of memory. *Journal of Verbal Learning and Verbal Behavior, 22*(3), 261–295. http://dx.doi.org/10.1016/S0022-5371(83)90201-3.

Anderson, K. C., & Insel, T. R. (2006). The promise of extinction research for the prevention and treatment of anxiety disorders. *Biological Psychiatry, 60*(4), 319–321. http://dx.doi.org/10.1016/j.biopsych.2006.06.022.

Anderson, C., & Platten, C. R. (2011). Sleep deprivation lowers inhibition and enhances impulsivity to negative stimuli. *Behavioural Brain Research, 217*(2), 463–466. http://dx.doi.org/10.1016/j.bbr.2010.09.020.

Antony, J. W., Gobel, E. W., O'Hare, J. K., Reber, P. J., & Paller, K. A. (2012). Cued memory reactivation during sleep influences skill learning. *Nature Neuroscience, 15*(8), 1114–1116. http://dx.doi.org/10.1038/nn.3152.

Antrobus, J. (1983). REM and NREM sleep reports: Comparison of word frequencies by cognitive classes. *Psychophysiology, 20*(5), 562–568.

Aserinsky, E., & Kleitman, N. (1953). Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science (New York, N.Y.), 118*(3062), 273–274.

Babkoff, H., Genser, S. G., Sing, H. C., Thorne, D. R., & Hegge, F. W. (1985). The effects of progressive sleep loss on a lexical decision task: Response lapses and response accuracy. *Behavior Research Methods, Instruments, and Computers, 17*, 614.

Babkoff, H., Thorne, D. R., Sing, H. O. C., Genser, S. G., Taube, S. L., & Hegge, F. W. (1985). Dynamic changes in work/rest duty cycles in a study of sleep deprivation. *Behavior Research Methods, Instruments, and Computers, 17*, 604–613.

Baglioni, C., Battagliese, G., Feige, B., Spiegelhalder, K., Nissen, C., Voderholzer, U., et al. (2011). Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. *Journal of Affective Disorders, 135*(1–3), 10–19. http://dx.doi.org/10.1016/j.jad.2011.01.011.

Balon, R. (1996). Bupropion and nightmares. *The American Journal of Psychiatry, 153*(4), 579–580.

Baran, B., Pace-Schott, E. F., Ericson, C., & Spencer, R. M. (2012). Processing of emotional reactivity and emotional memory over sleep. *The Journal of Neuroscience, 32*(3), 1035–1042. http://dx.doi.org/10.1523/JNEUROSCI.2532-11.2012.

Barbera, J. (2008). Sleep and dreaming in Greek and Roman philosophy. *Sleep Medicine, 9*(8), 906–910. http://dx.doi.org/10.1016/j.sleep.2007.10.010.

Barrett, D. (1993). The "committee of sleep": A study of dream incubation for problem solving. *Dreaming, 3*(2), 115.

Bartlett, S. F. (1932). *Remembering*. Oxford: University Press.

Blagrove, M. (2009). Dreaming – motivated or meaningless? *The Psychologist, 22*(8), 680–683.
Bowden, E. M., & Jung-Beeman, M. (2003). Aha! Insight experience correlates with solution activation in the right hemisphere. *Psychonomic Bulletin & Review, 10*(3), 730–737.
Braun, A. R., Balkin, T. J., Wesenten, N. J., Carson, R. E., Varga, M., Baldwin, P., et al. (1997). Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study. *Brain: A Journal of Neurology, 120*(Pt 7), 1173–1197.
Broese, M., Riemann, D., Hein, L., & Nissen, C. (2012). Alpha-Adrenergic receptor function, arousal and sleep: Mechanisms and therapeutic implications. *Pharmacopsychiatry, 45*(6), 209–216. http://dx.doi.org/10.1055/s-0031-1299728.
Brown, A. S., & Marsh, E. J. (2008). Evoking false beliefs about autobiographical experience. *Psychonomic Bulletin & Review, 15*(1), 186–190.
Burton, S. A., Harsh, J. R., & Badia, P. (1988). Cognitive activity in sleep and responsiveness to external stimuli. *Sleep, 11*(1), 61–68.
Buzsaki, G. (1996). The hippocampo-neocortical dialogue. *Cerebral Cortex (New York, N.Y.: 1991), 6*(2), 81–92.
Cai, D. J., Mednick, S. A., Harrison, E. M., Kanady, J. C., & Mednick, S. C. (2009). REM, not incubation, improves creativity by priming associative networks. *Proceedings of the National Academy of Sciences of the United States of America, 106*(25), 10130–10134. http://dx.doi.org/10.1073/pnas.0900271106.
Cairney, S. A., Durrant, S. J., Power, R., & Lewis, P. A. (2014). Complementary roles of slow-wave sleep and rapid eye movement sleep in emotional memory consolidation. *Cerebral Cortex (New York, N.Y.: 1991)*. http://dx.doi.org/10.1093/cercor/bht349.
Callaway, C. W., Lydic, R., Baghdoyan, H. A., & Hobson, J. A. (1987). Pontogeniculooccipital waves: Spontaneous visual system activity during rapid eye movement sleep. *Cellular and Molecular Neurobiology, 7*(2), 105–149.
Cartwright, R. D. (1974). Problem solving: Waking and dreaming. *Journal of Abnormal Psychology, 83*(4), 451–455.
Cartwright, R. D. (1983). Rapid eye movement sleep characteristics during and after mood-disturbing events. *Archives of General Psychiatry, 40*(2), 197–201.
Cartwright, R., Baehr, E., Kirkby, J., Pandi-Perumal, S. R., & Kabat, J. (2003). REM sleep reduction, mood regulation and remission in untreated depression. *Psychiatry Research, 121*(2), 159–167.
Castren, E. (2005). Is mood chemistry? *Nature Reviews. Neuroscience, 6*(3), 241–246. http://dx.doi.org/10.1038/nrn1629.
Cavallero, C., Cicogna, P., Natale, V., Occhionero, M., & Zito, A. (1992). Slow wave sleep dreaming. *Sleep, 15*(6), 562–566.
Chase, M. H., & Morales, F. R. (1990). The atonia and myoclonia of active (REM) sleep. *Annual Review of Psychology, 41*, 557–584. http://dx.doi.org/10.1146/annurev.ps.41.020190.003013.
Cicogna, P. C., & Bosinelli, M. (2001). Consciousness during dreams. *Consciousness and Cognition, 10*(1), 26–41. http://dx.doi.org/10.1006/ccog.2000.0471.
Cote, K. A., Mondloch, C. J., Sergeeva, V., Taylor, M., & Semplonius, T. (2014). Impact of total sleep deprivation on behavioural neural processing of emotionally expressive faces. *Experimental Brain Research, 232*(5), 1429–1442. http://dx.doi.org/10.1007/s00221-013-3780-1.
Craske, M. G., Kircanski, K., Zelikowsky, M., Mystkowski, J., Chowdhury, N., & Baker, A. (2008). Optimizing inhibitory learning during exposure therapy. *Behaviour Research and Therapy, 46*(1), 5–27. http://dx.doi.org/10.1016/j.brat.2007.10.003.
Datta, S. (1997). Cellular basis of pontine ponto-geniculo-occipital wave generation and modulation. *Cellular and Molecular Neurobiology, 17*(3), 341–365.
Datta, S. (1999). PGO wave generation: Mechanism and functional significance. In B. N. Mallick & S. Inoue (Eds.), *Rapid eye movement sleep* (pp. 91–106). New Delhi: Narosa Publishing House.
Datta, S., & O'Malley, M. W. (2013). Fear extinction memory consolidation requires potentiation of pontine-wave activity during REM sleep. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 33*(10), 4561–4569. http://dx.doi.org/10.1523/JNEUROSCI.5525-12.2013.
David, D., de Faria, L., Lapeyra, O., & Mellman, T. A. (2004). Adjunctive risperidone treatment in combat veterans with chronic PTSD. *Journal of Clinical Psychopharmacology, 24*(5), 556–559.
de Koninck, J., Lorrain, D., Christ, G., Proulx, G., & Coulombe, D. (1989). Intensive language learning and increases in rapid eye movement sleep: Evidence of a performance factor. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology, 8*(1), 43–47.
Deliens, G., Gilson, M., Schmitz, R., & Peigneux, P. (2013a). Sleep unbinds memories from their emotional context. *Cortex; A Journal Devoted to the Study of the Nervous System and Behavior, 49*(8), 2221–2228. http://dx.doi.org/10.1016/j.cortex.2012.11.014.
Deliens, G., Leproult, R., Neu, D., & Peigneux, P. (2013b). Rapid eye movement and non-rapid eye movement sleep contributions in memory consolidation and resistance to retroactive interference for verbal material. *Sleep, 36*(12), 1875–1883. http://dx.doi.org/10.5665/sleep.3220.
Deliens, G., Neu, D., & Peigneux, P. (2013c). Rapid eye movement sleep does not seem to unbind memories from their emotional context. *Journal of Sleep Research, 22*(6), 656–662. http://dx.doi.org/10.1111/jsr.12065.
Deliens, G., & Peigneux, P. (2014). One night of sleep is insufficient to achieve sleep-to-forget emotional decontextualisation processes. *Cognition & Emotion, 28*(4), 698–706. http://dx.doi.org/10.1080/02699931.2013.844105.
Dement, W., & Kleitman, N. (1957). Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. *Electroencephalography and Clinical Neurophysiology, 9*(4), 673–690.
Desseilles, M., Dang-Vu, T. T., Sterpenich, V., & Schwartz, S. (2011). Cognitive and emotional processes during dreaming: A neuroimaging view. *Consciousness and Cognition, 20*(4), 998–1008. http://dx.doi.org/10.1016/j.concog.2010.10.005.
Diekelmann, S., & Born, J. (2010). The memory function of sleep. *Nature Reviews. Neuroscience, 11*(2), 114–126. http://dx.doi.org/10.1038/nrn2762.
Dinges, D. F. (1990). Are you awake? Cognitive performance and reverie during the hypnopompic state. In R. Bootzin, J. Kihlstrom, & D. Schacter (Eds.), *Sleep and cognition*. Washington, D.C.: American Psychological Association.
Dolcos, F., LaBar, K. S., & Cabeza, R. (2005). Remembering one year later: Role of the amygdala and the medial temporal lobe memory system in retrieving emotional memories. *Proceedings of the National Academy of Sciences of the United States of America, 102*(7), 2626–2631. http://dx.doi.org/10.1073/pnas.0409848102.
Ellenbogen, J. M., Hu, P. T., Payne, J. D., Titone, D., & Walker, M. P. (2007). Human relational memory requires time and sleep. *Proceedings of the National Academy of Sciences of the United States of America, 104*(18), 7723–7728. http://dx.doi.org/10.1073/pnas.0700094104.
Fenn, K. M., Nusbaum, H. C., & Margoliash, D. (2003). Consolidation during sleep of perceptual learning of spoken language. *Nature, 425*(6958), 614–616. http://dx.doi.org/10.1038/nature01951.
Flanagan, O. J. (2000). *Dreaming souls: Sleep, dreams, and the evolution of the conscious mind*. Oxford: Oxford University Press.
Fosse, M. J., Fosse, R., Hobson, J. A., & Stickgold, R. J. (2003). Dreaming and episodic memory: A functional dissociation? *Journal of Cognitive Neuroscience, 15*(1), 1–9. http://dx.doi.org/10.1162/089892903321107774.
Foulkes, W. D. (1962). Dream reports from different stages of sleep. *Journal of Abnormal and Social Psychology, 65*, 14–25.
Foulkes, D. (1966). *The psychology of sleep*. New York: Charles Scribner's Sons.
Foulkes, D. (1985). *Dreaming: A cognitive-psychological analysis*. New Jersey: L. Erlbaum Associates.
Franzen, P. L., Buysse, D. J., Dahl, R. E., Thompson, W., & Siegle, G. J. (2009). Sleep deprivation alters pupillary reactivity to emotional stimuli in healthy young adults. *Biological Psychology, 80*(3), 300–305. http://dx.doi.org/10.1016/j.biopsycho.2008.10.010.
Freud, S. (1955). *The interpretation of dreams* (J. Strachey, Trans. & Ed.). New York: Basic Books.
Fu, J., Li, P., Ouyang, X., Gu, C., Song, Z., Gao, J., et al. (2007). Rapid eye movement sleep deprivation selectively impairs recall of fear extinction in hippocampus-independent tasks in rats. *Neuroscience, 144*(4), 1186–1192. http://dx.doi.org/10.1016/j.neuroscience.2006.10.050.
Gaillard, J. M., & Moneme, A. (1977). Modification of dream content after preferential blockade of mesolimbic and mesocortical dopaminergic systems. *Journal of Psychiatric Research, 13*(4), 247–256.
Giles, D. E., Kupfer, D. J., Rush, A. J., & Roffwarg, H. P. (1998). Controlled comparison of electrophysiological sleep in families of probands with unipolar depression. *The American Journal of Psychiatry, 155*(2), 192–199.
Girardeau, G., Benchenane, K., Wiener, S. I., Buzsaki, G., & Zugaro, M. B. (2009). Selective suppression of hippocampal ripples impairs spatial memory. *Nature Neuroscience, 12*(10), 1222–1223. http://dx.doi.org/10.1038/nn.2384.
Giuditta, A., Ambrosini, M. V., Montagnese, P., Mandile, P., Cotugno, M., Grassi Zucconi, G., et al. (1995). The sequential hypothesis of the function of sleep. *Behavioural Brain Research, 69*(1–2), 157–166.
Giuditta, A., Ambrosini, M. V., Scaroni, R., Chiurulla, C., & Sadile, A. (1985). Effect of sleep on cerebral DNA synthesized during shuttle-box avoidance training. *Physiology & Behavior, 34*(5), 769–778.
Goder, R., Baier, P. C., Beith, B., Baecker, C., Seeck-Hirschner, M., Junghanns, K., et al. (2013). Effects of transcranial direct current stimulation during sleep on memory performance in patients with schizophrenia. *Schizophrenia Research, 144*(1–3), 153–154. http://dx.doi.org/10.1016/j.schres.2012.12.014.
Gottesmann, C., & Gottesman, I. (2007). The neurobiological characteristics of rapid eye movement (REM) sleep are candidate endophenotypes of depression, schizophrenia, mental retardation and dementia. *Progress in Neurobiology, 81*(4), 237–250. http://dx.doi.org/10.1016/j.pneurobio.2007.01.004.
Graves, L. A., Heller, E. A., Pack, A. I., & Abel, T. (2003). Sleep deprivation selectively impairs memory consolidation for contextual fear conditioning. *Learning & Memory (Cold Spring Harbor, N.Y.), 10*(3), 168–176. http://dx.doi.org/10.1101/lm.48803.
Groch, S., Wilhelm, I., Diekelmann, S., & Born, J. (2013). The role of REM sleep in the processing of emotional memories: Evidence from behavior and event-related potentials. *Neurobiology of Learning and Memory, 99*, 1–9. http://dx.doi.org/10.1016/j.nlm.2012.10.006.
Gruart-Masso, A., Nadal-Alemany, R., Coll-Andreu, M., Portell-Cortes, I., & Marti-Nicolovius, M. (1995). Effects of pretraining paradoxical sleep deprivation upon two-way active avoidance. *Behavioural Brain Research, 72*(1–2), 181–183.
Gujar, N., McDonald, S. A., Nishida, M., & Walker, M. P. (2011a). A role for REM sleep in recalibrating the sensitivity of the human brain to specific emotions. *Cerebral Cortex (New York, N.Y.: 1991), 21*(1), 115–123. http://dx.doi.org/10.1093/cercor/bhq064.
Gujar, N., Yoo, S.-S., Hu, P., & Walker, M. P. (2011b). Sleep deprivation amplifies reactivity of brain reward networks, biasing the appraisal of positive emotional experiences. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 31*(12), 4466–4474. http://dx.doi.org/10.1523/JNEUROSCI.3220-10.2011.
Halberstadt, L., Haeffel, G. J., Abramson, L. Y., Mukherji, B. R., Metalsky, G. I., & Dykman, B. M. (2008). Schematic processing: A comparison of clinically

Please cite this article in press as: Landmann, N., et al. REM sleep and memory reorganization: Potential relevance for psychiatry and psychotherapy. *Neurobiology of Learning and Memory* (2015), http://dx.doi.org/10.1016/j.nlm.2015.01.004

depressed, dysphoric, and nondepressed college students. *Cognitive Therapy and Research, 32*, 843–855.

Harrison, Y., & Horne, J. A. (1999). One night of sleep loss impairs innovative thinking and flexible decision making. *Organizational Behavior and Human Decision Processes, 78*(2), 128–145. http://dx.doi.org/10.1006/obhd.1999.2827.

Hartley, D. (1801). *Observations on Akan, his frame, his duty and his expectations*. London: Johnson.

Hauner, K. K., Howard, J. D., Zelano, C., & Gottfried, J. A. (2013). Stimulus-specific enhancement of fear extinction during slow-wave sleep. *Nature Neuroscience, 16*(11), 1553–1555. http://dx.doi.org/10.1038/nn.3527.

Hermans, D., Craske, M. G., Mineka, S., & Lovibond, P. F. (2006). Extinction in human fear conditioning. *Biological Psychiatry, 60*(4), 361–368. http://dx.doi.org/10.1016/j.biopsych.2005.10.006.

Hervey de Saint-Denys, M. J. L. (1867/1977). *Les Rêves et les moyens de les diriger*. Paris: Editions D'Aujourd'hui.

Hobson, J. A. (2009). REM sleep and dreaming: Towards a theory of protoconsciousness. *Nature Reviews. Neuroscience, 10*(11), 803–813. http://dx.doi.org/10.1038/nrn2716.

Hobson, J. A., & McCarley, R. W. (1977). The brain as a dream state generator: An activation-synthesis hypothesis of the dream process. *The American Journal of Psychiatry, 134*(12), 1335–1348.

Hobson, J. A., Pace-Schott, E. F., & Stickgold, R. (2000). Dreaming and the brain: Toward a cognitive neuroscience of conscious states. *The Behavioral and Brain Sciences, 23*(6), 793–842. Discussion 904–1121.

Horne, J. A. (1988). Sleep loss and "divergent" thinking ability. *Sleep, 11*(6), 528–536.

Howell, M. J. (2012). Parasomnias: An updated review. *Neurotherapeutics: The Journal of the American Society for Experimental Neurotherapeutics, 9*(4), 753–775. http://dx.doi.org/10.1007/s13311-012-0143-8.

Jakovljevic, M., Sagud, M., & Mihaljevic-Peles, A. (2003). Olanzapine in the treatment-resistant, combat-related PTSD–a series of case reports. *Acta Psychiatrica Scandinavica, 107*(5), 394–396. Discussion 396.

Johnson, M. K., Kahan, T. L., & Raye, C. L. (1984). Dreams and reality monitoring. *Journal of Experimental Psychology. General, 113*(3), 329–344.

Jones, B. (2005). Basic mechanisms of sleep-wake states. *Principles and Practice of Sleep Medicine*, 136–153.

Kaplan, C. A., & Simon, H. A. (1990). In search of insight. *Cognitive Psychology, 22*, 374–419.

Kleim, B., Wilhelm, F. H., Temp, L., Margraf, J., Wiederhold, B. K., & Rasch, B. (2014). Sleep enhances exposure therapy. *Psychological Medicine, 44*(7), 1511–1519. http://dx.doi.org/10.1017/S0033291713001748.

Krakow, B., & Zadra, A. (2006). Clinical management of chronic nightmares: Imagery rehearsal therapy. *Behavioral Sleep Medicine, 4*(1), 45–70. http://dx.doi.org/10.1207/s15402010bsm0401_4.

Kumar, T., & Jha, S. K. (2012). Sleep deprivation impairs consolidation of cued fear memory in rats. *PLoS ONE, 7*(10), e47042. http://dx.doi.org/10.1371/journal.pone.0047042.

Lambert, M. T. (2006). Aripiprazole in the management of post-traumatic stress disorder symptoms in returning Global War on Terrorism veterans. *International Clinical Psychopharmacology, 21*(3), 185–187. http://dx.doi.org/10.1097/01.yic.0000185021.48279.00.

Landmann, N., Kuhn, M., Piosczyk, H., Feige, B., Baglioni, C., Spiegelhalder, K., et al. (2014). The reorganisation of memory during sleep. *Sleep Medicine Reviews*. http://dx.doi.org/10.1016/j.smrv.2014.03.005.

Lara-Carrasco, J., Nielsen, T. A., Solomonova, E., Levrier, K., & Popova, A. (2009). Overnight emotional adaptation to negative stimuli is altered by REM sleep deprivation and is correlated with intervening dream emotions. *Journal of Sleep Research, 18*(2), 178–187. http://dx.doi.org/10.1111/j.1365-2869.2008.00709.x.

Lavie, P. (2001). Sleep disturbances in the wake of traumatic events. *The New England Journal of Medicine, 345*(25), 1825–1832. http://dx.doi.org/10.1056/NEJMra012893.

Lavie, P., & Hobson, J. A. (1986). Origin of dreams: Anticipation of modern theories in the philosophy and physiology of the eighteenth and nineteenth centuries. *Psychological Bulletin, 100*(2), 229–240.

Lewis, P. A., & Durrant, S. J. (2011). Overlapping memory replay during sleep builds cognitive schemata. *Trends in Cognitive Sciences, 15*(8), 343–351. http://dx.doi.org/10.1016/j.tics.2011.06.004.

Llinas, R., & Ribary, U. (1993). Coherent 40-Hz oscillation characterizes dream state in humans. *Proceedings of the National Academy of Sciences of the United States of America, 90*(5), 2078–2081.

Manni, R. (2005). Rapid eye movement sleep, non-rapid eye movement sleep, dreams, and hallucinations. *Current Psychiatry Reports, 7*(3), 196–200.

Maquet, P. (2005). Current status of brain imaging in sleep medicine. *Sleep Medicine Reviews, 9*(3), 155–156. http://dx.doi.org/10.1016/j.smrv.2005.01.003.

Maquet, P., Peters, J., Aerts, J., Delfiore, G., Degueldre, C., Luxen, A., et al. (1996). Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. *Nature, 383*(6596), 163–166. http://dx.doi.org/10.1038/383163a0.

Maquet, P., Ruby, P., Maudoux, A., Albouy, G., Sterpenich, V., Dang-Vu, T., et al. (2005). Human cognition during REM sleep and the activity profile within frontal and parietal cortices: A reappraisal of functional neuroimaging data. *Progress in Brain Research, 150*, 219–227. http://dx.doi.org/10.1016/S0079-6123(05)50016-5.

Marks, G. A., Shaffery, J. P., Oksenberg, A., Speciale, S. G., & Roffwarg, H. P. (1995). A functional role for REM sleep in brain maturation. *Behavioural Brain Research, 69*(1–2), 1–11.

Marsh, E. J., Tversky, B., & Hutson, M. (2005). How eyewitnesses talk about events: Implications for memory. *Applied Cognitive Psychology, 19*(5), 531–544. http://dx.doi.org/10.1002/acp.1095.

Marshall, L., Helgadottir, H., Molle, M., & Born, J. (2006). Boosting slow oscillations during sleep potentiates memory. *Nature, 444*(7119), 610–613. http://dx.doi.org/10.1038/nature05278.

Mazzarello, P. (2000). What dreams may come? *Nature, 408*(6812), 523. http://dx.doi.org/10.1038/35046170.

McCarley, R. W., Winkelman, J. W., & Duffy, F. H. (1983). Human cerebral potentials associated with REM sleep rapid eye movements: Links to PGO waves and waking potentials. *Brain Research, 274*(2), 359–364.

McCullough, J. P. (2000). *Treatment for chronic depression: Cognitive behavioral analysis system of psychotherapy (CBASP)*. New York: Guilford Press.

McCullough, J. P. (2006). *Treating chronic depression with disciplined personal involvement. Cognitive behavioral analysis system of psychotherapy (CBASP)*. New York: Springer.

McNamara, P., Auerbach, S., Johnson, P., Harris, E., & Doros, G. (2010). Impact of REM sleep on distortions of self-concept, mood and memory in depressed/anxious participants. *Journal of Affective Disorders, 122*(3), 198–207. http://dx.doi.org/10.1016/j.jad.2009.06.030.

Mednick, S. A. (1962). The associative basis of the creative process. *Psychological Review, 69*, 220–232.

Mellman, T. A., Pigeon, W. R., Nowell, P. D., & Nolan, B. (2007). Relationships between REM sleep findings and PTSD symptoms during the early aftermath of trauma. *Journal of Traumatic Stress, 20*(5), 893–901. http://dx.doi.org/10.1002/jts.20246.

Menz, M. M., Rihm, J. S., Salari, N., Born, J., Kalisch, R., Pape, H. C., et al. (2013). The role of sleep and sleep deprivation in consolidating fear memories. *NeuroImage, 75*, 87–96. http://dx.doi.org/10.1016/j.neuroimage.2013.03.001.

Merritt, J., Stickgold, R., Pace-Schott, E., Williams, J., & Hobson, J. A. (1994). Emotion profiles in the dreams of men and women. *Consciousness and Cognition, 3*, 46–60.

Metcalfe, J., & Wiebe, D. (1987). Intuition in insight and noninsight problem solving. *Memory & Cognition, 15*(3), 238–246.

Miyauchi, S., Misaki, M., Kan, S., Fukunaga, T., & Koike, T. (2009). Human brain activity time-locked to rapid eye movements during REM sleep. *Experimental Brain Research, 192*(4), 657–667. http://dx.doi.org/10.1007/s00221-008-1579-2.

Moore, B. A., & Krakow, B. (2007). Imagery rehearsal therapy for acute posttraumatic nightmares among combat soldiers in Iraq. *The American Journal of Psychiatry, 164*(4), 683–684. http://dx.doi.org/10.1176/appi.ajp.164.4.683.

National Sleep Foundation. (2002). *The 2002 "sleep in America" poll: Adult sleep habits*. Retrieved from <http://sleepfoundation.org/sleep-polls-data/sleep-in-america-poll/2002-adult-sleep-habits>.

Ngo, H.-V. V., Martinetz, T., Born, J., & Molle, M. (2013). Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. *Neuron, 78*(3), 545–553. http://dx.doi.org/10.1016/j.neuron.2013.03.006.

Nielsen, T. A. (2000). A review of mentation in REM and NREM sleep: "Covert" REM sleep as a possible reconciliation of two opposing models. *The Behavioral and Brain Sciences, 23*(6), 851–866. Discussion 904–1121.

Nielsen, T. A., Deslauriers, D., & Baylor, G. W. (1991). Emotions in dream and waking event reports. *Dreaming, 1*, 287–300.

Nielsen, T., & Levin, R. (2007). Nightmares: A new neurocognitive model. *Sleep Medicine Reviews, 11*(4), 295–310. http://dx.doi.org/10.1016/j.smrv.2007.03.004.

Nishida, M., Pearsall, J., Buckner, R. L., & Walker, M. P. (2009). REM sleep, prefrontal theta, and the consolidation of human emotional memory. *Cerebral Cortex (New York, N.Y.: 1991), 19*(5), 1158–1166. http://dx.doi.org/10.1093/cercor/bhn155.

Nissen, C., Nofzinger, E. A., Feige, B., Waldheim, B., Radosa, M.-P., Riemann, D., et al. (2006a). Differential effects of the muscarinic M1 receptor agonist RS-86 and the acetylcholine-esterase inhibitor donepezil on REM sleep regulation in healthy volunteers. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 31*(6), 1294–1300. http://dx.doi.org/10.1038/sj.npp.1300906.

Nissen, C., Power, A. E., Nofzinger, E. A., Feige, B., Voderholzer, U., Kloepfer, C., et al. (2006b). M1 muscarinic acetylcholine receptor agonism alters sleep without affecting memory consolidation. *Journal of Cognitive Neuroscience, 18*(11), 1799–1807. http://dx.doi.org/10.1162/jocn.2006.18.11.1799.

Nofzinger, E. A., Mintun, M. A., Wiseman, M., Kupfer, D. J., & Moore, R. Y. (1997). Forebrain activation in REM sleep: An FDG PET study. *Brain Research, 770*(1–2), 192–201.

Pace-Schott, E. F., & Hobson, J. A. (2002). The neurobiology of sleep: Genetics, cellular physiology and subcortical networks. *Nature Reviews. Neuroscience, 3*(8), 591–605. http://dx.doi.org/10.1038/nrn895.

Pace-Schott, E. F., Verga, P. W., Bennett, T. S., & Spencer, R. M. (2012). Sleep promotes consolidation and generalization of extinction learning in simulated exposure therapy for spider fear. *Journal of Psychiatric Research, 46*(8), 1036–1044. http://dx.doi.org/10.1016/j.jpsychires.2012.04.015.

Payne, J. D., & Kensinger, E. A. (2011). Sleep leads to changes in the emotional memory trace: Evidence from FMRI. *Journal of Cognitive Neuroscience, 23*(6), 1285–1297. http://dx.doi.org/10.1162/jocn.2010.21526.

Payne, J. D., Schacter, D. L., Propper, R. E., Huang, L.-W., Wamsley, E. J., Tucker, M. A., et al. (2009). The role of sleep in false memory formation. *Neurobiology of Learning and Memory, 92*(3), 327–334. http://dx.doi.org/10.1016/j.nlm.2009.03.007.

Please cite this article in press as: Landmann, N., et al. REM sleep and memory reorganization: Potential relevance for psychiatry and psychotherapy. *Neurobiology of Learning and Memory* (2015), http://dx.doi.org/10.1016/j.nlm.2015.01.004

Payne, J. D., Stickgold, R., Swanberg, K., & Kensinger, E. A. (2008). Sleep preferentially enhances memory for emotional components of scenes. *Psychological Science, 19*(8), 781–788. http://dx.doi.org/10.1111/j.1467-9280.2008.02157.x.

Peirano, P. D., & Algarin, C. R. (2007). Sleep in brain development. *Biological Research, 40*(4), 471–478.

Perogamvros, L., Dang-Vu, T. T., Desseilles, M., & Schwartz, S. (2013). Sleep and dreaming are for important matters. *Frontiers in Psychology, 4*, 474. http://dx.doi.org/10.3389/fpsyg.2013.00474.

Phelps, E. A., & LeDoux, J. E. (2005). Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron, 48*(2), 175–187. http://dx.doi.org/10.1016/j.neuron.2005.09.025.

Pinter, M. M., Pogarell, O., & Oertel, W. H. (1999). Efficacy, safety, and tolerance of the non-ergoline dopamine agonist pramipexole in the treatment of advanced Parkinson's disease: A double blind, placebo controlled, randomised, multicentre study. *Journal of Neurology, Neurosurgery, and Psychiatry, 66*(4), 436–441.

Plihal, W., & Born, J. (1997). Effects of early and late nocturnal sleep on declarative and procedural memory. *Journal of Cognitive Neuroscience, 9*(4), 534–547. http://dx.doi.org/10.1162/jocn.1997.9.4.534.

Popa, D., Duvarci, S., Popescu, A. T., Lena, C., & Pare, D. (2010). Coherent amygdalocortical theta promotes fear memory consolidation during paradoxical sleep. *Proceedings of the National Academy of Sciences of the United States of America, 107*(14), 6516–6519. http://dx.doi.org/10.1073/pnas.0913016107.

Power, A. E. (2004). Slow-wave sleep, acetylcholine, and memory consolidation. *Proceedings of the National Academy of Sciences of the United States of America, 101*(7), 1795–1796. http://dx.doi.org/10.1073/pnas.0400237101.

Quirk, G. J., & Mueller, D. (2008). Neural mechanisms of extinction learning and retrieval. *Biological Psychiatry, 33*(1), 56–72. http://dx.doi.org/10.1038/sj.npp.1301555.

Rao, V., McCann, U., Han, D., Bergey, A., & Smith, M. T. (2014). Does acute TBI-related sleep disturbance predict subsequent neuropsychiatric disturbances? *Brain Injury: [BI], 28*(1), 20–26. http://dx.doi.org/10.3109/02699052.2013.847210.

Rasch, B., & Born, J. (2013). About sleep's role in memory. *Physiological Reviews, 93*(2), 681–766. http://dx.doi.org/10.1152/physrev.00032.2012.

Rasch, B., Buchel, C., Gais, S., & Born, J. (2007). Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science (New York, N.Y.), 315*(5817), 1426–1429. http://dx.doi.org/10.1126/science.1138581.

Revonsuo, A. (2000). The reinterpretation of dreams: An evolutionary hypothesis of the function of dreaming. *The Behavioral and Brain Sciences, 23*(6), 877–901. Discussion 904–1121.

Reynolds, C. F., Buysse, D. J., Kupfer, D. J., Hoch, C. C., Houck, P. R., Matzzie, J., et al. (1990). Rapid eye movement sleep deprivation as a probe in elderly subjects. *Archives of General Psychiatry, 47*(12), 1128–1136.

Reynolds, C. F., III, Hoch, C. C., Buysse, D. J., Houck, P. R., Schlernitzauer, M., Frank, E., et al. (1992). Electroencephalographic sleep in spousal bereavement and bereavement-related depression of late life. *Biological Psychiatry, 31*(1), 69–82.

Reynolds, C. F. 3., Hoch, C. C., Buysse, D. J., Houck, P. R., Schlernitzauer, M., Pasternak, R. E., et al. (1993). Sleep after spousal bereavement: A study of recovery from stress. *Biological Psychiatry, 34*(11), 791–797.

Riemann, D., Berger, M., & Voderholzer, U. (2001). Sleep and depression–results from psychobiological studies: An overview. *Biological Psychology, 57*(1–3), 67–103.

Rittenhouse, C. D., Stickgold, R., & Hobson, J. A. (1994). Constraint on the transformation of characters, objects, and settings in dream reports. *Consciousness and Cognition, 3*(1), 100–113.

Ritter, S. M., Strick, M., Bos, M. W., van Baaren, Rick B., & Dijksterhuis, A. (2012). Good morning creativity: Task reactivation during sleep enhances beneficial effect of sleep on creative performance. *Journal of Sleep Research, 21*(6), 643–647. http://dx.doi.org/10.1111/j.1365-2869.2012.01006.x.

Rothbaum, B. O., & Davis, M. (2003). Applying learning principles to the treatment of post-trauma reactions. *Annals of the New York Academy of Sciences, 1008*, 112–121.

Rudoy, J. D., Voss, J. L., Westerberg, C. E., & Paller, K. A. (2009). Strengthening individual memories by reactivating them during sleep. *Science (New York, N.Y.), 326*(5956), 1079. http://dx.doi.org/10.1126/science.1179013.

Sanford, L. D., Silvestri, A. J., Ross, R. J., & Morrison, A. R. (2001). Influence of fear conditioning on elicited ponto-geniculo-occipital waves and rapid eye movement sleep. *Archives italiennes de biologie, 139*(3), 169–183.

Saper, C. B., Scammell, T. E., & Lu, J. (2005). Hypothalamic regulation of sleep and circadian rhythms. *Nature, 437*(7063), 1257–1263. http://dx.doi.org/10.1038/nature04284.

Schacter, D. L. (1999). The seven sins of memory. Insights from psychology and cognitive neuroscience. *The American Psychologist, 54*(3), 182–203.

Schacter, D. L., Chiao, J. Y., & Mitchell, J. P. (2003). The seven sins of memory: Implications for self. *Annals of the New York Academy of Sciences, 1001*, 226–239.

Schredl, M., & Erlacher, D. (2007). Self-reported effects of dreams on waking-life creativity: An empirical study. *The Journal of Psychology, 141*(1), 35–46. http://dx.doi.org/10.3200/JRLP.141.1.35-46.

Schwartz, S. (2003). Are life episodes replayed during dreaming? *Trends in Cognitive Sciences, 7*(8), 325–327.

Schwartz, S., & Maquet, P. (2002). Sleep imaging and the neuro-psychological assessment of dreams. *Trends in Cognitive Sciences, 6*(1), 23–30.

Silvestri, A. J. (2005). REM sleep deprivation affects extinction of cued but not contextual fear conditioning. *Physiology & Behavior, 84*(3), 343–349. http://dx.doi.org/10.1016/j.physbeh.2004.11.011.

Sio, U. N., Monaghan, P., & Ormerod, T. (2013). Sleep on it, but only if it is difficult: Effects of sleep on problem solving. *Memory & Cognition, 41*(2), 159–166. http://dx.doi.org/10.3758/s13421-012-0256-7.

Smith, C. (1985). Sleep states and learning: A review of the animal literature. *Neuroscience and Biobehavioral Reviews, 9*(2), 157–168.

Smith, C., & Lapp, L. (1987). Increased number of REMs following an intensive learning experience in college students. *Sleep Research, 16*, 211.

Solms, M. (1997). *The neuropsychology of dreams: A clinico-anatomical study*. Mahwah, NJ: Erlbaum.

Spoormaker, V. I., Schroter, M. S., Andrade, K. C., Dresler, M., Kiem, S. A., Goya-Maldonado, R., et al. (2012). Effects of rapid eye movement sleep deprivation on fear extinction recall and prediction error signaling. *Human Brain Mapping, 33*(10), 2362–2376. http://dx.doi.org/10.1002/hbm.21369.

Spoormaker, V. I., Sturm, A., Andrade, K. C., Schroter, M. S., Goya-Maldonado, R., Holsboer, F., et al. (2010). The neural correlates and temporal sequence of the relationship between shock exposure, disturbed sleep and impaired consolidation of fear extinction. *Journal of Psychiatric Research, 44*(16), 1121–1128. http://dx.doi.org/10.1016/j.jpsychires.2010.04.017.

Steriade, M., Amzica, F., & Contreras, D. (1996). Synchronization of fast (30–40 Hz) spontaneous cortical rhythms during brain activation. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 16*(1), 392–417.

Sterpenich, V., Albouy, G., Darsaud, A., Schmidt, C., Vandewalle, G., Dang, Vu., et al. (2009). Sleep promotes the neural reorganization of remote emotional memory. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 29*(16), 5143–5152. http://dx.doi.org/10.1523/JNEUROSCI.0561-09.2009.

Stickgold, R. (2005). Sleep-dependent memory consolidation. *Nature, 437*(7063), 1272–1278. http://dx.doi.org/10.1038/nature04286.

Stickgold, R. (2007). Of sleep, memories and trauma. *Nature Neuroscience, 10*(5), 540–542. http://dx.doi.org/10.1038/nn0507-540.

Stickgold, R., Malia, A., Fosse, R., Propper, R., & Hobson, J. A. (2001). Brain-mind states: I. Longitudinal field study of sleep/wake factors influencing mentation report length. *Sleep, 24*(2), 171–179.

Stickgold, R., Scott, L., Rittenhouse, C., & Hobson, J. A. (1999). Sleep-induced changes in associative memory. *Journal of Cognitive Neuroscience, 11*(2), 182–193.

Stickgold, R., & Walker, M. P. (2013). Sleep-dependent memory triage: Evolving generalization through selective processing. *Nature Neuroscience, 16*(2), 139–145. http://dx.doi.org/10.1038/nn.3303.

Talamini, L. M., Bringmann, L. F., de Boer, M., & Hofman, W. F. (2013). Sleeping worries away or worrying away sleep? Physiological evidence on sleep-emotion interactions. *PLoS ONE, 8*(5), e62480. http://dx.doi.org/10.1371/journal.pone.0062480.

Tamminen, J., Payne, J. D., Stickgold, R., Wamsley, E. J., & Gaskell, M. G. (2010). Sleep spindle activity is associated with the integration of new memories and existing knowledge. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 30*(43), 14356–14360. http://dx.doi.org/10.1523/JNEUROSCI.3028-10.2010.

Thompson, D. F., & Pierce, D. R. (1999). Drug-induced nightmares. *The Annals of Pharmacotherapy, 33*(1), 93–98.

Tononi, G., & Cirelli, C. (2003). Sleep and synaptic homeostasis: A hypothesis. *Brain Research Bulletin, 62*(2), 143–150.

van der Helm, Els., Yao, J., Dutt, S., Rao, V., Saletin, J. M., & Walker, M. P. (2011). REM sleep depotentiates amygdala activity to previous emotional experiences. *Current Biology: CB, 21*(23), 2029–2032. http://dx.doi.org/10.1016/j.cub.2011.10.052.

Vogel, G. W., Vogel, F., McAbee, R. S., & Thurmond, A. J. (1980). Improvement of depression by REM sleep deprivation. New findings and a theory. *Archives of General Psychiatry, 37*(3), 247–253.

Vuilleumier, P. (2005). How brains beware: Neural mechanisms of emotional attention. *Trends in Cognitive Sciences, 9*(12), 585–594. http://dx.doi.org/10.1016/j.tics.2005.10.011.

Wagner, U., Degirmenci, M., Drosopoulos, S., Perras, B., & Born, J. (2005). Effects of cortisol suppression on sleep-associated consolidation of neutral and emotional memory. *Biological Psychiatry, 58*(11), 885–893. http://dx.doi.org/10.1016/j.biopsych.2005.05.008.

Wagner, U., Fischer, S., & Born, J. (2002). Changes in emotional responses to aversive pictures across periods rich in slow-wave sleep versus rapid eye movement sleep. *Psychosomatic Medicine, 64*(4), 627–634.

Wagner, U., Gais, S., & Born, J. (2001). Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. *Learning & Memory (Cold Spring Harbor, N.Y.), 8*(2), 112–119. http://dx.doi.org/10.1101/lm.36801.

Wagner, U., Hallschmid, M., Rasch, B., & Born, J. (2006). Brief sleep after learning keeps emotional memories alive for years. *Biological Psychiatry, 60*(7), 788–790. http://dx.doi.org/10.1016/j.biopsych.2006.03.061.

Walker, M. P. (2009). The role of sleep in cognition and emotion. *Annals of the New York Academy of Sciences, 1156*, 168–197. http://dx.doi.org/10.1111/j.1749-6632.2009.04416.x.

Walker, M. P., Liston, C., Hobson, J. A., & Stickgold, R. (2002). Cognitive flexibility across the sleep-wake cycle: REM-sleep enhancement of anagram problem solving. *Brain Research. Cognitive Brain Research, 14*(3), 317–324.

Walker, M. P., & van der Helm, Els. (2009). Overnight therapy? The role of sleep in emotional brain processing. *Psychological Bulletin, 135*(5), 731–748. http://dx.doi.org/10.1037/a0016570.

Wehrle, R., Czisch, M., Kaufmann, C., Wetter, T. C., Holsboer, F., Auer, D. P., et al. (2005). Rapid eye movement-related brain activation in human sleep: A functional magnetic resonance imaging study. *NeuroReport, 16*(8), 853–857.

Please cite this article in press as: Landmann, N., et al. REM sleep and memory reorganization: Potential relevance for psychiatry and psychotherapy. *Neurobiology of Learning and Memory* (2015), http://dx.doi.org/10.1016/j.nlm.2015.01.004

Wimmer Hoffmann Bonato & Moffitt (1992). The effects of sleep deprivation on divergent thinking and attention processes. *Journal of Sleep Research, 1*(4), 223–230.

Wittmann, L., Schredl, M., & Kramer, M. (2007). Dreaming in posttraumatic stress disorder: A critical review of phenomenology, psychophysiology and treatment. *Psychotherapy and Psychosomatics, 76*(1), 25–39. http://dx.doi.org/10.1159/000096362.

Yoo, S.-S., Gujar, N., Hu, P., Jolesz, F. A., & Walker, M. P. (2007). The human emotional brain without sleep–a prefrontal amygdala disconnect. *Current Biology: CB, 17*(20), R877–R878. http://dx.doi.org/10.1016/j.cub.2007.08.007.

Young, J. E., Klosko, J. S., & Weishaar, M. E. (2003). *Schema therapy: A practitioner's guide*. New York: Guilford Press.

Glossary of Terms

Memory strengthening: the veridical preservation of stored information

Memory reorganization: changes in memory content that are reflected by qualitatively new memories that have not been directly learned

Schema: mental framework for the organization and understanding of information that enables the extraction of rules or general concepts on a meta-level

Please cite this article in press as: Landmann, N., et al. REM sleep and memory reorganization: Potential relevance for psychiatry and psychotherapy. *Neurobiology of Learning and Memory* (2015), http://dx.doi.org/10.1016/j.nlm.2015.01.004